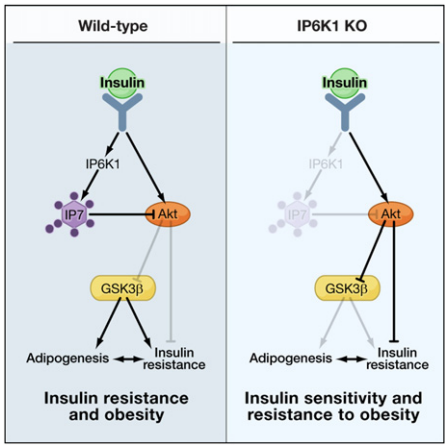
In This Issue

Cell



New Akt-Ins Diet

PAGE 897

Chakraborty et al. show that inositol pyrophosphate IP7 plays a key role in high-fat diet-induced insulin resistance and weight gain. Mechanistically, IP7 inhibits Akt kinase activation by blocking PH domain-mediated phosphorylation and membrane recruitment. Mice deficient for IP7 synthesis exhibit resistance to obesity induced by aging or high-fat diet. The results thus suggest that inhibitors of the kinase that generates IP7 may be beneficial for treatment of obesity and diabetes.

Cystic Fibrosis Revisited

PAGE 911

How does mutation of the CFTR chloride ion channel cause cystic fibrosis (CF)? Using a new porcine model of CF, Chen et al. see reduced chloride and bicarbonate flow across CF airway epithelia, as expected. However, in contrast to a widely held hypothesis, lack of CFTR does not increase sodium or liquid absorption. The data explain how loss of CFTR alters cellular electrical properties that had been previously interpreted as sodium hyperabsorption and clarify the initiating events in CF.

Ditching Your Sister, Finding Your Mate

PAGE 924

During meiosis, recombination occurs between homologous maternal and paternal chromosomes. Kim et al. investigate how interhomolog crossover is favored over crossovers between the two sister, or duplicate, chromatids that are also present. The authors find that, whereas the proteins that promote sister chromatid cohesion inhibit homolog recombination, the meiotic proteins Red1 and Mek1 counteract this effect to promote homolog recombination.

Adaptors Drive Ubiquitination Dynamics

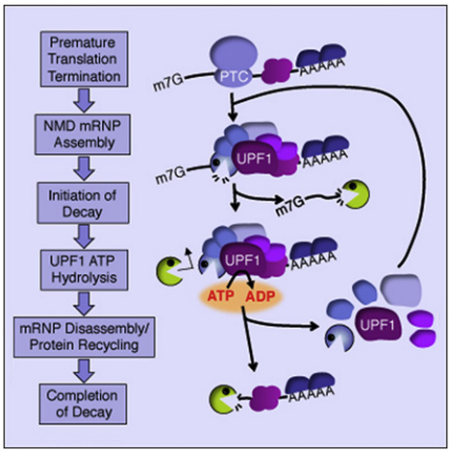
PAGE 951

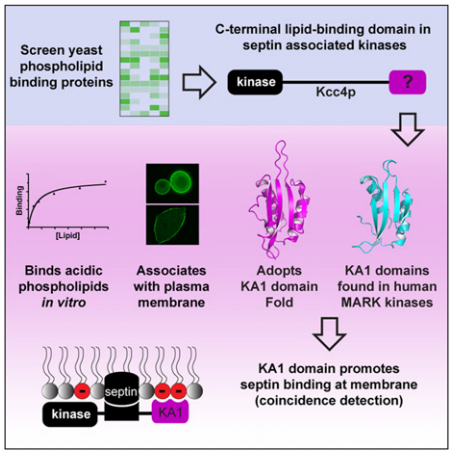
Cullin-RING ubiquitin ligases (CRLs) are modular ubiquitin ligases that rely on substrate adaptors to regulate degradation of specific proteins. In this issue, Bennett et al. analyze CRL complex dynamics in the cell with a novel quantitative proteomics platform. The authors find that the cellular abundance of substrate adaptors drives CRL network organization. These findings challenge the prevailing view that CRL complexes are principally regulated by cycles of deneddylation and complex disassembly.

mRNP Striptease

PAGE 938

The nonsense-mediated mRNA decay (NMD) pathway rids the cell of aberrant mRNAs with premature translation termination codons. Franks et al. demonstrate that disassembly of protein complexes from mRNAs targeted for NMD is required for complete mRNA degradation. This disassembly requires the ATPase activity of the Upf1 helicase and is critical for the recycling and reuse of NMD factors. These findings identify active disassembly of mRNPs as a critical step in mRNA decay.





New Tickets to the Membrane

PAGE 966

Spatial organization of cellular signaling relies on protein modules that interact with membrane surfaces. Moravcevic et al. now identify a new phospholipid-binding domain. A crystal structure reveals it to be a KA1 domain, seen in human MARK/PAR1 kinases implicated in disease. The results show that KA1 domains bind acidic phospholipids and, by cooperating with other binding modules, detect a coincidence of signals on membranes to target the kinases to specific subcellular locations.

Unusual Suspects in Redundancy

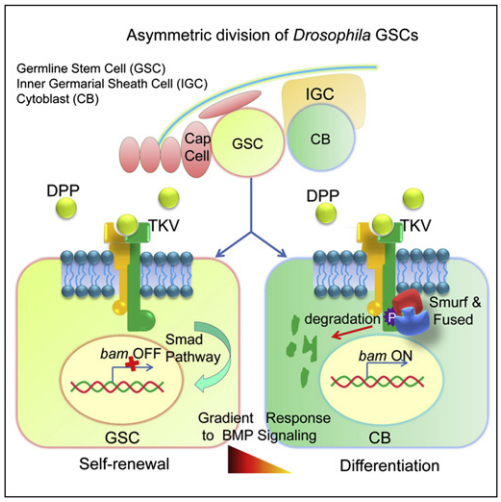
PAGE 991

Signaling networks include redundant components, such as homologous kinases, that compensate for each other when one component is lost. Could nonhomologous proteins, or even proteins of opposite function like kinases and phosphatases, compensate for each other, too? van Wageningen et al. develop a systems approach that not only identifies network redundancies involving nonhomologous proteins but also uncovers the molecular mechanisms generating such relationships. These findings explain how signaling pathways integrate to coordinate responses to stimuli.

Nearest Neighbors Are Miles apart in Signaling

PAGE 978

In the *Drosophila* ovary, germline stem cells (GSCs) divide asymmetrically to self-renew and produce daughter cytoblasts (CBs). GSCs are maintained by BMPs produced by niche cells. Xia et al. report a pathway for regulated proteolysis of the BMP receptor in CBs that generates a steep gradient of BMP activity between GSCs and the immediately adjacent CBs. This pathway confers divergent responses to secreted ligands to daughters just one cell diameter apart and allows CB differentiation.



Computing through Cancer's Complexity

PAGE 1005

Cancer genomes are extremely diverse from patient to patient, rendering identification of the genetic aberrations key for cancer initiation and progression challenging. Akavia et al. report a computational method that leverages DNA copy number and gene expression information to identify cancer drivers. Applying their method to a melanoma dataset, the authors revealed two genes involved in protein trafficking as drivers required for tumor cell proliferation.

Poly(A)-OK in Human RNAs

PAGE 1018

3′ untranslated regions and poly(A) tails orchestrate mRNA localization, stability, and translation. In this issue, Ozsolak et al. map genome-wide human and yeast polyadenylation states. From this analysis, they identify new sequence motifs correlated with human polyadenylation patterns and suggest that these position-specific sequences may be associated with polyadenylation of noncoding RNAs.